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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/603,713	06/27/2000	Jordan J.N. Tang	2932.1008-000	4604

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EXAMINER
MOHAMED, ABDEL A

ART UNIT	PAPER NUMBER
1653	16

DATE MAILED: 06/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/603,713	TANG ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the c ver sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *4,6-9,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,10-17 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT OF SEQUENCE LISTING, IDS, PRELIMINARY AMENDMENT, REPLY TO RESTRICTION REQUIREMENT AND STATUS OF THE CLAIMS

1. The Sequence Listing filed 6/27/00, Information Disclosure Statement and Form PTO-1449 filed 1/29/01, 3/12/01, 4/15/02 and 5/7/02, respectively and the preliminary amendment and response to restriction requirement filed 3/8/02 are acknowledged, entered and considered. With respect to the IDS and Form PTO-1449 filed 1/29/01 and 3/12/01, respectively, they are not considered and signed as requested by Applicant because the references cited therewith are not with the application. If Applicant intends for the Examiner to consider the IDS filed 1/29/01 and 3/12/01 (Paper Nos. 5 and 7, respectively), then, Applicant has to provide the references cited in the Form PTO-1449. Claims 1-23 are present for examination.

RESTRICTION OF SPECIES

2. It is noted that Applicant has elected Group II (claims 1-3 and 5-23) and Species OM99-2 with traverse on the reply to the restriction requirement filed 3/8/02 (Paper No. 11). However, based on telephonic interview of 3/4/02 (Paper No. 10) and telephonic election of 6/12/02, the restriction requirement of the previous Office action has been withdrawn by the Examiner and deemed to be moot in view of the new restriction of species.

ELECTION OF SPECIES

3. This application contains claims directed to the following patentably distinct species of the claimed invention: Species I, inhibitor OM99-1 (claim 4); Species II, inhibitor OM99-2 (claims 5, 11-15 and 21-23); Species III, inhibitor having the structure of Figure 10 (claim 6); Species IV, inhibitor having the structure of Figure 11 (claim 7); Species V, inhibitor having the structure of Figure 12 (claim 8); Species VI, inhibitor having the structure of Figure 13 (claim 9); and Species VII, inhibitor which is a non-amino acid small molecules (claims 18-19).

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-3, 10, 16-17 and 20 are generic to a plurality of disclosed patentably distinct species..

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

4. Because these inventions are distinct for the reasons given above and the search required for example of Species I , or II or III is not required for Species IV, or V, VI, or VII and vice versa because each of inhibitors of the species are patentably distinct from each other having various molecules and/or structures as recited in general formula of claim 3, Figures 10-13 of claims 6-9 and the inhibitors of claims 18-19, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Scott Pierce on 6/12/02 a provisional election was made with traverse to prosecute the invention of Species II, claims 5, 11-15 and 21-23. Affirmation of this election must be made by Applicant in replying to this Office action. Claims 4, 6-9 and 18-19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Thus, claims 4, 6-9 and 18-19 are withdrawn as non-elected species and the Office action is directed to the merits of claims 1-3, 5, 10-17 and 20-23 as per elected species.

OBJECTION TO TRADEMARK AND ITS USE

7. The use of the trademark "FPLC RESOURCE-Q™" has been noted in this application. Although, the use of trademark is permissible in patent applications, the proprietary nature of the mark should be respected and every effort made to prevent its use in a manner which might adversely affect its validity as trademark. Further, the specification which specifies the generic terminology should include published product information sufficient to show that the generic terminology or the generic description is inherent in the article referred by the trademark. This description requirement is made because the nature and composition of article denoted by trademark can change and affect the adequacy of the disclosure.

CLAIMS REJECTION-35 U.S.C. 112 [1st] PARAGRAPH.

8. Claims 1-3, 5, 10-17 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of memapsin 2 by OM99-1 and OM99-2 inhibitors and use of said inhibitors in designing, synthesizing and testing of inhibitory activity toward the enzyme *in vitro*, does not reasonably provide enablement for a product defined by reference to a desirable characteristic or property, namely that it is a memapsin 2 inhibitor by fitting the catalytic cleft of memapsin 2 as disclosed in claims 1-3 and 16-17 and to a method for treating a patient to decrease the likelihood of developing or progressing of Alzheimer's disease by administering to the individual an effective amount of memapsin 2 in the manner claimed in claims 21-23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not adequately teach an inhibitor of catalytically active memapsin 2 product defined by reference to a desirable characteristic or property by fitting into the catalytical cleft of memapsin 2 useful in diagnostic and for treatment and/or prevention of Alzheimer's disease as presently claimed in claims 1-3 and 10-17 and 21-23; rather, the specification teaches the use of memapsin 2 in a method of cloning (Example 1), distribution (Example 2), expression, refolding and purification (Example 3), proteolytic activity (Example 4), activation (Example 5), Expression in mammalian cells (Example 6), design and synthesis (Example 7), and measurement of enzymatic activity *in vitro* (Example 8).

Therefore, the instant specification does not commensurate with the claimed subject matter in which the compounds used as potent inhibitors of catalytically active memapsin 2 are expected to be particularly useful in the diagnostic and for treatment and/or prevention of Alzheimer's disease. Thus, there is no evidence or data to show that a similar regimen can be used for treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease by administering to the individual an effective amount of an inhibitor of memapsin 2 having an K_i of less than or equal to 10^{-7} M or which binds to crystallized enzyme characterized by the parameters in Table 2 when bound to OM99-2.

Thus, in view of the above, and in view of the fact that there is no enablement in the instant specification for the method of diagnosis and treating an/or preventing of Alzheimer's disease by administering the various inhibitors of memapsin 2 compounds claimed, and further in view of the complexity of Applicant's invention and the state of the art of diagnosing and treating and/or preventing of Alzheimer's disease, with the various compounds claimed; the Examiner is unable to determine the enablement of the invention as claimed without appropriate evidence or data. Such evidence in the art of treating cognitive dysfunctions details the state of the art in this area and establishes that even the disease is very hard to diagnose. For example, Ezzell (Scientific America, pages 152-153, March 7, 1993) states on page 152, middle column, before last paragraph that doctors can only diagnose Alzheimer's through a process of elimination, ruling out other disorders such as a slight stroke, a brain tumor, or even an adverse drug reaction. A definitive diagnosis must await death and autopsy, when a pathologist can view

the telltale "senile plaques" that pock the brains of Alzheimer's victim. Further, Varon et al. (Dev. Neurosci., Vol. 6, pp. 73-100, 1983/1984) discuss the implications of neurotrophic and neurite-promoting factor and their clinical potential in neuronal diseases such as Parkinson, ALS and Alzheimer in which the authors concluded by stating that further clinical progress requires a better understanding of neurobiological bases of nerve regeneration. Furthermore, Cordell et al. (U.S. Patent No. 5,221,607) discuss that the etiology of Alzheimer's disease is unknown and up to date, there are no means available to treat the pathogenesis of Alzheimer's disease and the paucity of understanding concerning the mechanism of amyloid formation in Alzheimer's disease is a major obstacle in the development and design of therapeutic agents that can intervene in this process (See e.g., Col.1, lines 55-67). Similarly, Nelson et al. (U.S. Patent No. 5,252,463) discuss serious diseases affecting the central nervous system which referred as neuropathologies such as Alzheimer's disease and Down's Syndrome in which the etiology of Alzheimer's disease is unknown (See e.g., column 1). Thus, the prior art clearly show the unpredictable nature and the complexity of the art in regard to diagnosis and treatment and/or prevention of Alzheimer's disease. Therefore, considering the nature of the diagnosis, treatment and/or prevention of Alzheimer's disease by administering the various inhibitors of memapsin 2 claimed and the limited success achieved; one skilled in the art would not accept the instantly claimed invention as obviously valid and correct without demonstration of evidence or data for the following reasons:

In view of the fact that animals and humans are outbred, in view of the lack of disclosure of suitable animal models for a method of diagnosing or treating or preventing cell death in the central or peripheral nervous system, in view of the recognized problems in the art regarding effective treatment of diseases affecting the nervous systems (neuropathologies) and in view of the fact that it is difficult to regenerate the neurons in the living body; a reasonable doubt exists as to the enablement of the claimed method of diagnosing or treating and/or preventing Alzheimer's disease in a subject and particularly in a human by administering the various inhibitors of memapsin 2 claimed. Thus, the claims are based on pure speculation that the method would be effective since Applicant has not established any *nexus* between the various claimed inhibitors of memapsin 2 and their use in the manner claimed.

Further, the first paragraph of 35 U.S.C. 112 requires, inter alia, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, in view of the above, and in view of the fact that there is no enablement in the instant specification for diagnosing and for treating and/or preventing Alzheimer's disease by administering various inhibitors of memapsin 2. Thus, applying the Wands factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Hence, in view of the quantity of experimentation necessary, the lack of adequate guidance or working examples or data, and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5, 10-17 and 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 5 and 10 are indefinite in failing to recite as to the function or activity or use of the inhibitor of memapsin 2 referred in claim 1 or claim 2 or claim 3 or claim 5 or claim 10 (i.e., it is not clear what the inhibitors recited in claims 1-3, 5 and 10 are supposed to do). Further, an attempt is made to define the product/inhibitor by reference to a result to be achieved (i.e., binds), and as such, clarity is lacking at the point of novelty since the novelty appears to be the inhibitor OM99-2 (SEQ ID NO:28 octapeptide). Thus, Applicant has to point out and distinctly claim the subject matter which is novel.

Claim 3 is indefinite in the recitation "L0-" and "P1' ", respectively. It is believed to be typographical error. Amendment of the claim to recite "L_0" and "P_1' ", respectively would obviate this rejection.

Claims 11 and 21 are indefinite and confusing in referring back to parameters in Table 2 in the specification because referring back to a Table or a Figure or a Number is not acceptable claim language. Such material should be incorporated within the claim language. Further, it is long standing Office practice that claims should be completed and self-contained and incorporation into claims by express reference to the specification is not permitted and should not be relied on to define the invention (*Ex parte Fressola*, Bd. Pat. Appl. & Inter., 5/11/93, p. 1608).

Claim 15 recites the limitation "amino acids 18-379 of memapsin 2" in lines 2-3. There is insufficient antecedent basis for this limitation in claim 1 or claim 11 or claim 15.

Claim 20 is indefinite in failing to recite a method step(s) because the claim is directed to "A method of synthesis of a Leu*Ala dipeptide isostere". Appropriate correction is required.

Claim 21 is indefinite in the recitation "....administering to the individual an effective amount...." because it is not clear what is meant by the terms "effective amount" since no amount of an inhibitor is claimed or disclosed, and as such, the metes and bounds of the claims cannot be determined.

Claim 23 is indefinite in the recitation the acronym "APP". Use of the full terminology at least in the first occurrence would obviate this rejection.

CLAIMS REJECTION-35 U.S.C. 102(b)

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 10 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Chrysler et al. (U.S. Patent No. 5,744,346).

The instantly claimed invention as claimed in claims 1-2, 10 and 16-17 is directed to an inhibitor of memapsin 2 (beta-secretase) which binds to the active site of the memapsin 2 comprising an isostere having an K_i of less than or equal to 10^{-7} M, wherein the inhibitor is permeable to the blood brain barrier and blocks cleavage by memapsin 2 under physiological conditions.

Similarly, the reference of Chrysler et al. discloses a beta-secretase (memapsin 2) inhibitor which binds to the active site of beta-secretase and as the result inhibiting proteolytic cleavage of APP which is employed in screening assay to identify beta-secretase inhibitors useful in the treatment of Alzheimer's disease and pharmaceutical formulations thereof (See e.g. abstract and summary of the invention). With respect to claims 2 and 10, the claims are directed solely to information and therefore are inherent to the general inhibitors claimed, since the inhibitor is not defined, and as such, anticipates claims 1-2, 10 and 16-17 as drafted.

CONCLUSION AND FUTURE CORRESPONDENCE

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher S. F. Low

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